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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/410,462	10/01/1999	ANGELICA WILLIAMS	ONYX1046-ORD	6889

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/410,462	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-13,15,17-20,22,23 and 26-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *6-13,15,17-20,22,23 and 26-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/28/2006 has been entered.

Claims 6-13, 15, 17-20, 22, 23, 26-34 are currently pending and are examined herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 1/20/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6, 7, 11-13, 15, 17, 18 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by anticipated by U.S. Patent No. 6,080,578 (Bischoff et al., previously of record).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Bischoff et al. teach a cytopathic adenoviral comprising a mutation in an E1A CR2 RB family member binding region as well as methods of using the vector for preferential therapy and prophylaxis of neoplasia compared to non-neoplastic cells (e.g., column 3, lines 7-29; column 4, lines 1-55; etc.) Bischoff et al. teach that the mutant adenoviral vector can comprise a mutation can be a e.g., a deletion, substitution frameshift in CR2 domain, amino acids 120-139 (see column 10, lines 10-25), and specifically teaches a mutant comprising a deletion of amino acids 2-150 (dl 1010) which completely deletes the CR1 and CR2 domains (see column 10, lines 25-40). Bischoff et al. teach that the mutant adenoviral vectors can be used to treat various different tumors in a subject by directly administering the vector to the tumor, for instance by swabbing a solution comprising the vector directly on a tumor or by direct injection (e.g., see column 16, lines 26-53). It is noted that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor, as well as non-dividing non-cancerous cells. Therefore, administering the vector taught by Bischoff to a subject having a tumor would necessarily result in substantially and selectively

killing dividing endothelial cells (including dividing microvasculature) and cancer cells in the subject.

Therefore, Bischoff et al. anticipates the instant claims.

Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Whyte et al. (J. Virol. 1988, previously of record).

The instant claim is drawn to a pharmaceutical composition comprising an Rb binding site adenoviral mutant in physiological solution where said adenoviral mutant is dl922/947.

Whyte teaches several mutant adenoviral vectors including the dl922/947 vector (e.g., see Figure 4) and further teaches that the vectors were administered to cells in tissue culture (e.g., see page 258, column 2) thus indicating that the vectors were in a physiological solution (also see page 258, first column). Therefore, Whyte anticipates the instant claim.

Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Jelsma et al. (Virol. 1989, previously of record).

The instant claim is drawn to a pharmaceutical composition comprising an Rb binding site adenoviral mutant in physiological solution where said adenoviral mutant is dl1107.

Jelsma several mutant adenoviral vectors including the dl1107 vector (e.g., see Figure 1) and further teaches that the vectors were administered to cells in tissue culture (e.g., see Table 2) thus indicating that the vectors were in a physiological solution (also see page 121, second column). Therefore, Jelsma anticipates the instant claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-13, 15, 17-20, 22, 23 and 26-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: methods of selectively killing dividing cells in a population of dividing and quiescent cells by administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region directly to the target dividing cells, does not reasonably provide enablement for the full scope of the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is a method for killing dividing cells while not killing non-dividing cells by administering a mutant cytopathic adenovirus to a subject having said cells.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims are broad in the sense that they encompass any route of administration, including general systemic delivery and delivery of the adenovirus at a site distal to the target cells such that the adenovirus must travel through the subjects system to reach the target cells.

The instant claims are not fully enabled because the prior art recognizes that there are major caveats for non-direct delivery of therapeutic nucleic acids (including advenoviral vectors). For instance, he art recognizes that in vivo administration of therapeutic nucleic acids is plagues by inefficient delivery to the target cells due to many factors including the hosts immune response (e.g., see Dang et al. or Eck et al. previously of record).

With respect to adenoviral vectors, Green et al. (Cancer Gene Therapy, 2002; 9:1036-1042) teaches:

> "The development of a targeted adenoviral vector, which can be delivered systemically, is one of the major challenges facing cancer gene therapy. The virus is readily cleared from the bloodstream, can be neutralised by pre-existing antibodies, and has a permissive cellular tropism. Clinical studies using the ONYX virus have shown Limited efficacy, but there are several hurdles to overcome to achieve an effective tumor-specific systemic therapy. In this review, we have summarized the various strategies used to overcome the Limitations of adenoviral-mediated gene delivery." (See abstract).

Green et al. also notes that:

> "In clinical trials using ONYX-015, the majority of patients presented with neutralizing antibodies and almost all showed a significant increase in titer after the initial virus injection. There are also significant concerns over vector immunogenicity following the death of a patient after hepatic artery infusion of a replication-defective Ad vector. It is

thought that viral capsid proteins are involved in the acute cytokine release observed shortly after virus administration." (p. 1039, references omitted).

The specification provides examples which indicates that the mutant adenovirus can selectively kill dividing cells (and not quiescent cells) in vitro (Examples 1 and 2). Example 3 indicates that the mutant virus was delivered by direct injection into tumors of athymic mice and resulted in tumor regression (see Figure 4). The specification provides a working example (Example 4) which discloses intranasal inoculations of the mutant or wild type adenovirus to a immunocompetent rat and indicates that the intranasally administered mutant adenovirus divides less in the quiescent lung cells than the wild type virus. It is noted that intranasal delivery directly delivers the virus to lung tissue cells. Example 4 does not demonstrate that the intranasal administrtation of the mutant adenorial vector results in substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells. Furthermore, as previously pointed out, the claims encompass treating any tumor by any route of administration. As such, in order for the specification to be enabling for the full scope encompassed by the claims it would have to demonstrate that intranasal delivery could be used to specifically and effectively deliver the mutant adenoviral vectors to the target tumor cells wherein the target tumor cells can be any type of tumor such as a brain tumor such that the method results in substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells. The specification does not provide any such disclosure.

The level of the skill in the art is deemed to be high.

Considering the breadth of the claims (any route of administration), the state of the prior art at the time filing in view of the examples and guidance provided in the specification, it is clear that additional experimentation would be required to be able to predictably practice the

claimed method to the full scope encompassed by the claims. The additional experimentation would be trial and error experimentation to attempt to overcome the caveats taught in the prior art. Overcoming these obstacles would amount to an inventive step(s) over the prior art. Therefore, it is concluded that the specification does not provide an enabling disclosure for the instant claims and additional experimentation is required. The amount of additional experimentation is not routine and amounts to an undue amount of additional experimentation

Response to Arguments

Applicant's arguments, see pages 5-16 of the communication filed 1/20/2006 with respect to the rejection(s) of claim(s) under 35 USC 112, first paragraph have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a completely new ground(s) of rejection is made herein for the reasons indicated above.

Applicant's arguments, with respect to the rejection of claims under 35 USC 112, second paragraph have been fully considered and are persuasive. The rejection has been withdrawn.

With respect to the rejection of claims 1-6 under 35 USC 102(e), it is noted that claims 1-5 have been canceled, thus rending the rejection of these claims moot. Claim 6 has been amended such that it depends on claim 11. The rejection of claims under 35 USC 102(e) is considered a new grounds of rejection as it encompasses a different claim set.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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